REMARKS

A check for the fees for a five (5) month extension of time and for filing an RCE accompanies this response. An Information Disclosure Statement is filed herewith. Any fees that may be due in connection with the filing of this and the attached papers may be charged to Deposit Account No. 06-1050. If a Petition for Extension of Time is required, this paper is to be considered such Petition.

Claims 1, 3-21, 23-38, 40-76, 78-83, 87-89, 93 and 99-122 are pending herein. Claims 65-68 have been withdrawn from consideration as allegedly being drawn to a non-elected species. Claims 65-68 should be rejoined upon allowance of a generic claim, such as one that that recites a " a steroidal anti-inflammatory agent" or other claim that links the elected claims to withdrawn claims 65-68. Hence claims 65-68 are retained.

Claim 122, which finds basis throughout the specification and in the original claims, is added. Claims 1 and 3 are amended herein for clarity, and claims 2 and 77 are cancelled without prejudice or disclaimer. Applicant reserves the right to file continuation or divisional applications to any canceled subject matter. Applicant reserves the right to file continuation or divisional applications to any canceled subject matter.

Claim 1 is amended to emphasize that the composition is propellant-free. Basis for this amendment can be found throughout the specification. For example, a pharmacologically suitable fluid is defined on page 9 as suitable for pharmacological use but "not a propellant or gas." Claim 1 also is amended to incorporate claim 2; and claim 3 is amended to depend from claim 1 rather than cancelled claim 2.

Claim 78 is amended to render it clear that the composition is sufficiently stable to be provided in a kit, and claims 87-89 are amended to restore the language that the composition can be used for prevention of bronchoconstriction. Formoterol, inhaled steroids and combinations thereof are well-known agents for the prevention of bronchoconstriction. The instant claims are directed to formulations of drugs that have known effects. Formoterol and inhaled steroids are known and in fact are labeled to be used for prevention of bronchoconstriction. Attached are printouts that include the labeling information for formoterol as provided in the Physicians Desk Reference (see, also, articles attached hereto, which document the prophylactic effects of formoterol and corticosteroids). Similarly inhaled corticosteroids are administered as prophylactics as are combinations of $beta_2$ adrenergics (*i.e.*, Advair^R).

Attached are:

1) PubMed Abstract of Sovijarvi *et al.* (1992) *Respiration 59*:279-282;

2) PubMed Abstract of Boner *et al.* (1994) *Am J Respir Crit Care Med. 149*:935-939;

3) PubMed Abstract of McAlpine *et al.* (1990) *Respir Med 84*:293-295;

4) PubMed Abstract of Andersson *et al.* (1982) *Br. J Pharmacol.76*:139-147;

5) PubMed Abstract of Gauvreau *et al.* (1996) *Am J Respir Crit Care Med. 154*:1267-1271; and

6) PDRhealth describing indications for Foradil (generic name formoterol) and Pulmicort (generic name budesonide).

Telephonic Interview

The Examiner is thanked for the her courtesy extended in granting a telephonic interview on January 10, 2006. During the interview U.S. Patent No. 6,667,344, which is commonly assigned, and which is based on U.S. Application Serial No. 10/138,866, was discussed. U.S. Patent No. 6,667,344 includes claims that are generic to the claims pending in the instant application. An Office Action, mailed May 20, 2003, issued in connection with the above-captioned application was made of record in U.S. Application Serial No. 10/138,866, which was subsequently allowed. The Examiner is reminded that issued patents are presumed valid (35 U.S.C. § 282); Examiners are precluded from commenting on or impugning the validity of an issued patent (see MPEP § 1701, Office Personnel Not To Express Opinion on Validity or Patentability of Patent).

Declaration under 37 C.F.R. §1.132 and the instant "invention."

With respect to the Declaration of Partha Banerjee (inventor), submitted September 27, 2004, under 37 CFR 1.132, the Examiner states that it does not "demonstrate criticality of a claimed range of the concentration of formoterol in the claimed composition." It respectfully is submitted that the declaration was submitted to demonstrate that formoterol at a concentration for direct administration is not stable in aqueous compositions; it was not provided to present a comparison with the prior art (Hochrainer *et al.*) The concentration of formoterol in the instant compositions is that which is suitable for direct administration. The instant application describes that, contrary to the understanding in the art, stable aqueous, propellant-free, compositions formulated for direct administration can be prepared.

Hochrainer *et al.* teaches that its concentrates are stable; applicant has not disputed this. Hochrainer *et al.* also specifically teaches that its diluted compositions for direct administration are not stable. Hochrainer *et al.* teaches that formoterol compositions

formulated at a concentration for direct administration to a subject in need thereof are *not* stable. See, for example, column 1, lines 30-35, of Hochrainer *et al.*, which states:

> In the past it has been found that liquid aerosol formulations of formoterol are *not suitable* for use in inhalers intended for ambulatory inhalation treatment *since formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.* (emphasis added)

Hochrainer *et al.* further teaches that its concentrate is to be diluted prior to use, and that the diluted compositions (the "pharmaceutical preparations") are not stable during long term storage (only 10% remaining after 3 months at 40 °C in an exemplified composition).

Hence a Declaration to demonstrate that aqueous compositions of formoterol at concentrations for direct administration are not stable is not needed (no *prima facie* case of obviousness has been set forth), since this information is well known to those of skill in the art. In fact., it is the reason that all commercially available formoterol formulations are powder forms or concentrates or compositions in which the formoterol is provided in a non-aqueous composition or phase. In fact, Hochrainer *et al.* teaches that this is a problem (see above) and also column 1, lines 30-37:

> In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time. For this reason, formoterol has previously only been used in powder form for inhalation therapy.

Hochrainer *et al.* provides a solution to this problem; Hochrainer *et al.* provides concentrated compositions of formoterol that are ***not*** for direct administration.

Other publications and patents discuss this issue. For example, U.S. Patent No. 6,719,994 states:

> Formoterol is a drug belonging to the class of $beta_2$-agonists, characterized by rapid onset of broncho-dilating action which lasts for many hours. For the treatment of asthma, Formoterol is usually administered through the inhalatory route by means of the so called dry powder inhalers (DPI), storable under normal ambient conditions, or in form of suspensions or solutions by means of pressurized metered dose inhalers, *which should be stored in refrigerator, in view of the above discussed poor stability of the active ingredients in aqueous medium.* [emphasis added]

U.S. Patent No. 6,719,994 solves the problem by:

> The present invention solves the problems concerning active ingredient stability, dosage uniformity and tolerability of the formulation to the lungs, by

> applying the technology of capsule production to the container system for the extemporaneous reconstitution of a solution immediately before use

Hence, the instability of formoterol in aqueous compositions is well known and a Declaration demonstrating such should not be needed.

The instant claims are directed to *aqueous* compositions containing formoterol at concentrations for direct administration (*i.e.*, no dilution before administration) that are stable for long-term storage. As discussed below, prior to the instant application, there was no suggestion in the art that it would be possible to prepare an aqueous composition containing formoterol for direct administration that is sufficiently stable to be provided as a pharmaceutical.

The instant application teaches parameters that should be varied to achieve this result; varying such parameters and testing for stability is within the skill in the art. Prior to the instant application there would have been no motivation to do so, since it was believed that formoterol, at concentrations for direct administration, is too rapidly degraded in aqueous compositions. For this reason, a Declaration comparing the stability of a particular composition disclosed in the instant application is more stable than a composition of Hochrainer *et al.* is not needed. The instant application teaches a variety of parameters that can be varied to produce a stable aqueous composition of formoterol at a concentration for direct administration. It is not necessarily the fact that any particular composition is stable that confers patentability (Applicant is not conceding that particular compositions are not patentable), but it is the fact that, *despite a belief in the art*, including the cited art, to the contrary, the instant application demonstrates that it is possible to prepare a stable aqueous composition of formoterol at a concentration for direct administration such and guarantee the pharmaceutical quality of the formulation over lengthy periods of time. This is *precisely* what Hochrainer *et al.* teaches is not possible (col. 1, lines 30-37):

> In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time. For this reason, formoterol has previously only been used in powder form for inhalation therapy.

Therefore, as discussed below, a *prima facie* case of obviousness has not been set forth.

REJECTION OF CLAIMS 1-21, 23-38, 40-64,69-83, 87-89, 93 and 99-121 UNDER 35 U.S.C. §103

Claims 1-21, 23-38, 40-64, 69-83, 87-89, 99-112 and 117-119

Claims 1-21, 23-38, 40-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103 as being unpatentable over Carling *et al.* (U.S. Patent No. 5,674,860) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418) because Carling *et al.* teaches a pharmaceutical composition containing formoterol in combination with budesonide, but does not does not expressly disclose a pharmaceutical composition comprising water, and Hochrainer *et al.* teaches a pharmaceutical composition containing formoterol suitable for storage in water and ethanol. It is alleged that combination of these references results in the compositions of the instant claims. In particular the Examiner states that:

> [o]ne having ordinary skill in the art at the time the invention was made would have been motivated to employ water and ethanol and buffer solution in a inhalation composition, since water and ethanol and buffer solution are known to be used in the inhalation composition of Hochrainer *et al.* comprising formoterol in the aqueous solution with known pH ranges for the same inhalation therapy for suitable for stable storage. Thus, employing water, ethanol and buffer solution, and adjusting particular pH value by buffer, and adjusting the ionic strength of the composition by adding those inorganic and organic salts taught by Hochrainer *et al.* and Carling et al. are all deemed obvious since they are all within the knowledge and conventional skills in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See In re Boesch, 205 USPQ 215 (CCPA 1980).

This rejection is respectfully traversed.

Relevant Law

[I]n order to establish a prima facie case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the

modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The claims

Claim 1 is directed to a pharmaceutical composition, comprising (i) formoterol, or a pharmaceutically acceptable salt or hydrate thereof; and (ii) a steroidal anti-inflammatory agent, or a pharmaceutically acceptable salt or hydrate thereof. The composition is formulated for long term storage, and it is an aqueous composition in which the formoterol free base concentration is about 5 μg/mL to about 2 mg/mL so that the composition is formulated at a concentration for direct administration, and is propellant-free. Claims 1, 3-21, 23-38, 40-76, 78, 81- 83, 87-89, 93, 99-108 and 111-122 are dependent thereon.

Claim 78 is directed to an a kit that contains: (a) a propellant-free aqueous composition that contains (i) formoterol or a pharmaceutically acceptable salt or hydrate thereof, where the formoterol is present at a concentration of 5 μg/ml to about 2 mg/ ml; and (ii) a steroidal anti-inflammatory agent or a pharmaceutically acceptable salt or hydrate thereof, formulated for single dosage administration, where the aqueous composition has an estimated shelf-life of greater than 1 month usage time at 25 °C and greater than or equal to 1 year storage time at 5 °C; and (b) a nebulizer. Claims 79, 80, 109 and 110 are dependent on claim 78.

The teachings of the cited references and differences from the instant claims

Carling *et al.*,

Carling *et al.* teaches combination therapy using formoterol and budesonide in the treatment of asthma. Carling *et al.* teaches in Examples 1-3 dry powder inhalation formulations (DPI) and metered dose inhalation (MDI) formulations of the above-referenced combination. The DPI formulations are not aqueous compositions; the MDI formulations contain propellants. It does not teach or suggest nebulizable formulations of formoterol and budesonide that are propellant-free, have a formoterol concentration of between about 5 μg/mL and about 2 mg/mL, and that are stable during long term storage, as required by the instant claims. Further Carling *et al.* does not teach or suggest that aqueous compositions containing formoterol at concentrations for direct administration that are stable for long term storage can be prepared.

Hochrainer *et al.* does not cure this deficiency. As discussed above, Hochrainer *et al.* teaches that:

> it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time. For this reason, formoterol has previously only been used in powder form for inhalation therapy.

As a solution to this problem, Hochrainer *et al.* teaches Hochrainer *et al.* teaches two compositions: 1) an "active substance concentrate;" and 2) a "pharmaceutical preparation," which is prepared from the concentrate just prior to use.

"Active substance concentrate"

The "active substance concentrate" is taught as a "highly concentrated" solution or suspension (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) that is stable for a period of several months, possibly up to several years without any deterioration in the pharmaceutical quality (see, e.g., column 1, lines 55-61; column 2, lines 4-7; and claim 1 of Hochrainer et al.). Hence it is *not* formulated at a concentration for direct administration to a subject in need thereof. See, *e.g.,* column 2, lines 1-4:

As defined in Hochrainer *et al.* "highly concentrated" means a concentration of the active substance that is usually too high to permit the corresponding solution or suspension to be used therapeutically for inhalation without being diluted. See also, *e.g.,* column 1, lines 47-52:

> The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a pharmaceutical preparation (aerosol formulation) which is converted by means of a nebulizer into an inhalable aerosol.

See also, *e.g.*, column 4, lines 9-13:

> The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

Thus the "active substance concentrate" of Hochrainer *et al.* provides the solution to the problem that aqueous formulations of formoterol for direct administration are not stable.

Hochrainer *et al.* teaches highly concentrated compositions of formoterol suitable for storage. Hochrainer *et al.* teaches, at column 2, lines 4-11, that the concentration of

formoterol in the compositions taught therein is much higher – at least 10 mg/mL, preferably at least 75, 100 or 250 mg/mL:

> According to the invention the formoterol concentration in the active substance concentrate is between 10 mg/ml and 500 mg/ml. Preferably, the minimum concentration is at least 75 mg/ml. Preferred concentrations are between 100 mg/ml and 400 mg/ml, particularly between 250 mg/ml and 350 mg/ml.
>
> **"Pharmaceutical preparation"**

For use, the "active substance concentrate" is diluted for direct administration. Hochrainer *et al.* teaches that formoterol compositions formulated at a concentration for direct administration to a subject in need thereof are not stable. In Example 3 of Hochrainer *et al.*, it is stated that in the aqueous pharmaceutical preparation formoterol breaks down to 10% at 40° C within only 3 months. In contrast in the concentrated formulations, no breakdown was observed even after 6 months' storage at 40° C. Hochrainer *et al.* thus unequivocally states that formoterol cannot be stored in a sufficiently stable manner in am aqueous composition to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.

Hence, Hochrainer *et al.* teaches that aqueous compositions of formoterol for direct administration are not stable and teaches compositions that contain high concentrations of formoterol. Hochrainer *et al.* does not teach or suggest that aqueous compositions for direct administration can be prepared. Hochrainer *et al.* teaches that such compositions cannot be prepared. Thus, Hochrainer *et al.* does not cure the deficiencies in the teachings of Carling *et al.*

The combination of cited references does not teach or suggest that which applicant has done.

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992). In this instance, the combination of cited references does not result in the instantly claimed compositions, and further does not suggest any modification that would result in the instantly claimed compositions.

The Examiner urges:

> Hochrainer *et al.* discloses a pharmaceutical composition comprising formoterol particularly stable on storage with concentration 10-500 mg/ml. It is also known that the effective amount of formoterol in a pharmaceutical composition, is 6-100 μg, preferred 6-48 μg according to Carling *et al.* Thus, optimization of known effective amounts of known agents in the aqueous solution to be administered according the disclosures of Hochrainer *et al.* and Carling *et al.* is considered well in the competence level of an ordinary skilled artisan and within the knowledge and conventional skills in pharmaceutical science. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See In re Boesch, 205 USPQ 215 (CCPA 1980).

The Examiner's argument fails to address this issue. None of the cited references teaches or suggests that it is ***possible*** to prepare an aqueous composition for direct administration that is stable for long term storage; in fact they teach that such compositions are not stable. Hence it is irrelevant that optimization of the concentrations of known agents is within the level of the ordinarily skilled artisan. The references fail to teach or suggest the parameter, stability for long term storage, that is optimized. Absent that teaching, the combination of teachings of the cited references **cannot and do not result** in the instantly claimed compositions and kits.

With respect to the Declaration, as discussed above, the Declaration was not provided to describe comparative results, and further such data is not needed. Hochrainer *et al.* teaches that aqueous compositions of formoterol for direct administration are not stable and teaches that its diluted preparation is not stable.

Claims 1-21, 23-38, 40-64, 69-83, 87-89, 99-112 and 117-119

Claims 1-21, 23-38, 40-64,69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Blondino *et al.* (U.S. Patent No. 6,004,537) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418) because Blondino *et al.* teaches a pharmaceutical composition containing formoterol in combination with budesonide, but does not Blondino et al. does not teach a:

> pharmaceutical composition comprising water, and Blondino et al. does not expressly disclose that the concentration of formoterol in the aqueous solution is about 5μg/ml- 2 mg/ml, and buffer providing particular pH value, and the ionic strength of the composition.

The Examiner states that Hochrainer *et al.* teaches a pharmaceutical composition containing formoterol suitable for storage in water and ethanol and concludes that the combination of these references results in the compositions of the instant claims. This rejection is respectfully traversed.

Relevant Law

The relevant law is discussed above.

The claims

The claims are discussed above.

The teachings of the cited references and differences from the instant claims

Blondino *et al.* teaches combination therapy using formoterol and budesonide in the treatment of asthma. Blondino *et al.* teaches in the Examples MDI formulations (containing a fluoroalkane propellant) of the above-referenced combination. The cited reference does not teach or suggest nebulizable formulations containing formoterol and budesonide.

The Office Action points to the title, abstract and claims for the proposition that Blondino *et al.* teaches nebulizable formulations. Applicant respectfully disagrees. The entire teaching of Blondino *et al.* is directed to MDI formulations containing a fluoroalkane propellant. Notwithstanding the interpretation, the compositions of Blondino *et al.* address the problem of the instability of formoterol (and budesonide) by preparing compositions in which they are dissolved or solubilized in a mixture of cosolvent and propellant. Blondino *et al.* states (col. 2, lines 4-24):

> The present invention provides a novel pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation formulated from a composition comprising: Budesonide; Formoterol; at least one fluoroalkane propellant; and a cosolvent present in an amount that dissolves or solubilizes the budesonide and Formoterol in the mixture of cosolvent and propellant. The present invention also provides a novel solution aerosol formulation formulated from a composition comprising: Budesonide; Formoterol; at least one fluoroalkane propellant; and a cosolvent present in an amount that dissolves or solubilizes the Budesonide and Formoterol in the mixture of cosolvent and propellant.

Blondino *et al.* continues at column 2, lines 29-38:

> It has been unexpectedly discovered that chemically and physically stable aerosol formulations containing a mixture of Budesonide and Formoterol can be formulated utilizing high concentrations of cosolvent in which the mixture of Budesonide and Formoterol is dissolved or solubilized in the mixture of cosolvent and propellant. Budesonide and Formoterol aerosol formulations can be formed according to the present invention which exhibit enhanced stability under elevated temperatures (40° C.), thus requiring no refrigeration.

Hence, Blondino *et al.* provides compositions in which budesonide and formoterol are dissolved or solubilized in a mixture of cosolvent and propellants. Thus, Blondino does not teach or suggest *propellant-free aqueous formulations* of formoterol and budesonide that

contain formoterol concentration of between about 5 μg/mL and about 2 mg/mL for direct administration and that are stable during long term storage, as required by the instant claims.

Hochrainer *et al.* , as discussed above, does not cure this deficiency in the teachings of Blondino *et al.* Hochrainer *et al.* does not teach or suggest compositions having a formoterol concentration of between about 5 μg/mL and about 2 mg/mL that are stable during long term storage. As discussed in detail above, in contrast, Hochrainer *et al.* teaches that aqueous compositions of formoterol at concentrations for direct administration are not stable for long term storage. Therefore, Hochrainer *et al.* does not cure the defects in Blondino *et al.*, and the instant claims are not *prima facie* obvious over the teachings of Blondino *et al.* in view of Hochrainer *et al.*

The combination of teachings of Blondino *et al.* with those of Hochrainer *et al.*, does not result in the instantly claimed compositions and kits

The cited references, singly or in any combination thereof, do not teach or suggest that it is possible to prepare a propellant-free aqueous formulation of formoterol and budesonide that contains formoterol at a concentration of between about 5 μg/mL and about 2 mg/mL for direct administration and that is stable during long term storage. Absent such suggestion, the ordinarily skilled artisan would have had no motivation to do that which applicant has done. Therefore, the Examiner as failed to set forth a *prima facie* case of obviousness.

The Examiner states:

> One having ordinary skill in the art at the time the invention was made would have been motivated to employ water and ethanol and buffer solution in a inhalation composition, since water and ethanol and buffer solution are known to be used in the inhalation composition of Hochrainer et al. comprising formoterol for the same inhalation therapy as Blondino et al.
>
> Thus, employing water, ethanol and buffer solution, and adjusting particular pH value by buffer, and adjusting the ionic strength of the composition by adding those inorganic and organic salts taught by Hochrainer et al. are all deemed obvious since they are all within the knowledge and conventional skills in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect.

Applicant respectfully disagrees. Each of Blondino *et al.* and Hochrainer *et al.* teaches that compositions containing formoterol are not stable in aqueous compositions. Each addresses this problem in a different way. Hochrainer *et al.* prepares its concentrate and

Blondino *et al.* prepares a non-aqueous composition in which the formoterol and budesonide are dissolved or solubilized in cosolvent and propellant. Neither reference suggests that it is possible to "optimize" any parameters to achieve an aqueous propellant-free composition that is stable for long term storage. Therefore, it is irrelevant whether or not it is within the level of ordinary skill in the art to have optimized parameters; the cited references fail to teach or suggest the parameters to be optimized and both teach that it formoterol is not stable in aqueous compositions at concentrations for direct administration.

Claim 93

Claim 93 is rejected under 35 U.S.C. §103 as allegedly being unpatentable over Carling *et al.* (U.S. Patent No. 5,674,860) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418) and further in view of the Physician's Desk Reference entries for albuterol, accolate and Zyflo. It is alleged that combination of these references results in the compositions of the instant claim. This rejection is respectfully traversed.

Relevant Law

The relevant law is discussed above.

Instant claim 93

Instant claim 93 is directed to the pharmaceutical composition of claim 1, as described above, further containing one or more of (a) to (j) as follows: (a) a ß2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lypoxygenase inhibitor; or (j) an anti-IgE antibody.

The teachings of the cited references and differences from the instant claim

As discussed in detail above, while Carling *et al.* teaches or suggests nebulizable formulations containing formoterol and budesonide, it does not teach or suggest nebulizable formulations of formoterol and budesonide that have a formoterol concentration of between about 5 µg/mL and about 2 mg/mL, and are stable during long term storage, as required by the instant claim. Carling *et al.* does not teach or suggest that it is possible to prepare such a composition.

Hochrainer *et al.* does not cure this deficiency in the teachings of Carling *et al.* Hochrainer *et al.* does not teach or suggest aqueous propellant-free compositions having a formoterol concentration of between about 5 µg/mL and about 2 mg/mL for direct

administration that are stable during long term storage. As discussed above Hochrainer *et al.* does not cure the deficiencies in the teachings of Carling *et a.*

The cited PDR entries do not cure the deficiencies in the teachings of d Carling *et al.* or Hochrainer *et al.* The cited PDR entries simply state the known use of asthma drugs, but do not teach or suggest that it is possible to formulate aqueous compositions of formoterol and a steroidal anti-inflammatory agent, where the formoterol concentration is between about 5 μg/mL and about 2 mg/mL for direct administration, and where the composition is stable during long term storage.

Therefore, for the reasons discussed above with respect to independent claims 1 and 78 and claims dependent on each, the Examiner has failed to set forth a *prima facie* case of obviousness over the teachings of Carling *et al.* in view of Hochrainer *et al.* and further in view of the PDR entries for albuterol, accolate and Zyflo.

Claims 113-116 and 120-121

Claims 113-116 and 120-121 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Carling *et al.* (U.S. Patent No. 5,674,860) in view of Hochrainer *et al.* (U.S. Patent No. 6,150,418) and further in view of the Hardmann *et al.* (Goodman Gilman's *The Pharmacological Basis of Therapeutics*, **1996**, 665) or Leckie *et al.* (*Novel Therapy of COPD*, abstract, Jan. 2000). It is alleged that combination of these references results in the compositions of the instant claim. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116 and 120-121

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116, 120 and 121 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

The teachings of the cited references and differences from the instant claim

As discussed in detail above, the combination of Carling *et al.* and Hochrainer *et al.* do not teach or suggest the instantly claimed stable aqueous concentrated compositions of formoterol at concentrations for direct administration and suitable for long term storage. Neither Hardmann *et al.* nor Leckie *et al.* singly or in any combination thereof cure this deficiency in the teachings of Carling *et al.* and Hochrainer *et al.*

Hardman *et al.* teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma, but does not teach or suggest how to formulate combinations of this drug with formoterol and a steroidal anti-inflammatory agent for long term storage and direct administration. Leckie *et al.* teaches that tiotropium bromide is a known bronchodilator employed in treating asthma, but does not teach or suggest how to formulate combinations of this drug with formoterol and a steroidal anti-inflammatory agent as instantly claimed.

Therefore, the combination of teachings of Carling *et al.* in view of Hochrainer *et al.* and further in view of Hardmann *et al.* or Leckie *et al.* do not result in the instantly claimed compositions.

* * *

In view of the above, reconsideration and allowance are respectfully requested.

Respectfully submitted,

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1: Respiration. 1992;59(5):279-82. Related Articles, Links

Preventive effects of inhaled formoterol and salbutamol on histamine-induced bronchoconstriction--a placebo-controlled study.

Sovijarvi AR, Reinikainen K, Freudenthal Y, Andersson P, Riska H.

Department of Pulmonary Medicine, Helsinki University Central Hospital, Finland.

The preventive effects of inhaled formoterol (a new beta 2-agonist) and salbutamol aerosols on histamine-induced bronchoconstriction were studied in 12 patients with mild or moderate asthma in a placebo-controlled, double-blind study. Three hours after the administration of 12 micrograms formoterol, 200 micrograms salbutamol (doses with equal bronchodilator effects) or placebo via aerosol, histamine challenge was undertaken, using a dosimetric jet nebulizer with controlled tidal breathing. The noncumulative dose of histamine diphosphate aerosol provoking a 15% fall in FEV1 (PD15) was calculated. The PD15 after inhalation of 12 micrograms formoterol was significantly higher than that after 200 micrograms salbutamol (median values 640 and 310 micrograms, respectively; $p < 0.01$). For both treatments, the PD15 was significantly higher than that after placebo (median 185 micrograms). The results indicate that the preventive effect against histamine-induced bronchoconstriction at 3 h after drug is significantly better with formoterol than with salbutamol when using inhaled doses with an equal acute bronchodilator effect.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 1488561 [PubMed - indexed for MEDLINE]

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1: Am J Respir Crit Care Med. 1994 Apr;149(4 Pt 1):935-9. Related Articles, Links

Inhaled formoterol in the prevention of exercise-induced bronchoconstriction in asthmatic children.

Boner AL, Spezia E, Piovesan P, Chiocca E, Maiocchi G.

Pediatrics Department, University of Verona, Italy.

The duration and magnitude of the effect of inhaled formoterol (12 micrograms) against exercise-induced bronchoconstriction (EIB) was compared with that of inhaled salbutamol (200 micrograms) and that of placebo in 15 children with asthma and EIB in a double-blind, double-dummy, within-patient, placebo-controlled study. The treatments were given by metered dose aerosol on three different days. The exercise test was performed at the 3rd and the 12th hour after dosing. The magnitude of the blocking effect was assessed both by evaluating the lowest FEV1 reading obtained within an hour after each exercise test and by considering the percent decrease below the baseline FEV1 measured before drug administration. Comparison of the lowest values obtained during the hour after each exercise test shows that formoterol was significantly better than both salbutamol ($p = 0.022$), and placebo ($p = 0.001$) in limiting exercise-induced bronchoconstriction after the first exercise test (3 h after dosing), while no difference was observed between salbutamol and placebo ($p = 0.198$). After the second exercise test (12 h after dosing), formoterol again proved to be more effective than both salbutamol ($p = 0.008$) and placebo ($p = 0.001$), and no significant difference was observed between salbutamol and placebo ($p = 0.391$). The evaluation of the mean percentage decrease in FEV1 confirmed the results in favor of formoterol in both the exercise tests. No adverse effects were reported in any treatment group. The protection against EIB is significantly more prolonged after formoterol than after salbutamol, and persists for 12 h after dosing.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 7908246 [PubMed - indexed for MEDLINE]

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1: Respir Med. 1990 Jul;84(4):293-5. Related Articles, Links

Prophylaxis of exercise-induced asthma with inhaled formoterol, a long-acting beta 2-adrenergic agonist.

McAlpine LG, Thomson NC.

Department of Respiratory Medicine, Western Infirmary, Glasgow, U.K.

The prophylaxis of exercise-induced asthma with inhaled formoterol (12 micrograms) was compared with inhaled salbutamol (200 micrograms) and placebo in 12 patients with atopic asthma. Both drugs produced equal bronchodilation 2 and 4 h after administration. Both drugs protected equally against exercise-induced bronchoconstriction 2 h after administration; at 4 h, formoterol gave undiminished protection from that seen at 2 h while salbutamol was no more effective than placebo.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 2236756 [PubMed - indexed for MEDLINE]

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1: Br J Pharmacol. 1982 May;76(1):139-47. Related Articles, Links

Protective effects of the glucocorticoid, budesonide, on lung anaphylaxis in actively sensitized guinea-pigs: inhibition of IgE-but not of IgG-mediated anaphylaxis.

Andersson P, Brattsand R.

1 The effect of glucocorticoid pretreatment on antigen-induced bronchoconstriction was studied in guinea-pigs actively sensitized to two different ovalbumin regiments (one producing IgE- and IgG-like antibodies and the other exclusively IgG-like antibodies). 2 Budesonide (50 mg/kg) and hydrocortisone (50 mg/kg) given as one intraperitoneal injection 15-20 h before and anaphylactic tests or as two consecutive intraperitoneal injections 5 and 6 days before, led to a decreased bronchial capacity. In this respect glucocorticoid pretreatment was effective only in guinea-pigs sensitized to produce both IgE-like and IgG-like antibodies. 3 Budesonide pretreatment also reduced the capacity of anaphylactically-challenged chopped lung tissue to release histamine in guinea-pigs sensitized to produce both IgE- and IgG-like antibodies. 4 Budesonide pretreatment did not change the levels of circulating IgG1a and IgE-like homocytotropic antibodies as measured by passive cutaneous anaphylaxis; nor did it affect histamine or methacholine-induced bronchoconstriction in vivo or the capacity of histamine or methacholine to contract the guinea-pig isolated trachea preparation of the isoprenaline-induced relaxation of this preparation. 5 The selective inhibitory effects of budesonide and hydrocortisone on IgE-mediated but not IgG-mediated anaphylaxis and the relevance to human atopic disease are discussed.

PMID: 7082901 [PubMed - indexed for MEDLINE]

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1: Am J Respir Crit Care Med. 1996 Nov;154(5):1267-71. Related Articles, Links

Effects of inhaled budesonide on allergen-induced airway responses and airway inflammation.

Gauvreau GM, Doctor J, Watson RM, Jordana M, O'Byrne PM.

Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Allergen inhalation by sensitized subjects results in acute bronchoconstriction, which can be followed by a later bronchoconstrictor response, allergen-induced airway hyperresponsiveness, and increases in airway inflammatory cells. Treatment with inhaled glucocorticosteroids attenuates allergen-induced asthmatic airway responses. The purpose of this study was to determine whether a 1-wk pretreatment with inhaled budesonide influences allergen-induced changes in inflammatory cells in blood and induced sputum. Seven subjects with mild atopic asthma were treated in a double-blind, placebo-controlled, randomized, crossover fashion with either inhaled budesonide 400 microg/d, or placebo for 7 d. Allergen challenges were carried out the morning after treatment was discontinued and sputum samples were obtained 7 h after allergen inhalation. Methacholine airway responsiveness was measured, and blood and sputum samples were obtained 24 h post-allergen. Budesonide treatment attenuated the magnitude of both the early and the late asthmatic response, reduced allergen-induced methacholine airway hyperresponsiveness, and attenuated allergen-induced increases in total eosinophils and activated eosinophils. These results suggest that the effects of inhaled glucocorticosteroids on allergen-induced airway responses may be mediated through their inhibition of allergen-induced eosinophil migration and activation.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 8912734 [PubMed - indexed for MEDLINE]

Brand name:

Foradil

Pronounced: FOUR-a-dil
Generic name: Formoterol

Why is Foradil prescribed?

Foradil relaxes the muscles in the walls of the airways, allowing them to expand. Taken on a twice-daily basis, it helps to control asthma in people who need regular treatment with short-acting inhalers, including people with nighttime asthma. Regular twice-daily use can also relieve tightening of the airways in people with Chronic Obstructive Pulmonary Disease, including chronic bronchitis and emphysema.

Taken on an as-needed basis, Foradil can also be used to prevent exercise-induced tightening of the airways (also called "exercise-induced asthma") in adults and children 12 years of age and older.

Most important fact about Foradil

Foradil is used to *prevent* asthma attacks, and should not be used for the relief of acute asthma symptoms. Your doctor will prescribe a short-acting inhaler such as Proventil or Ventolin to use for acute asthma attacks.

How should you take Foradil?

Foradil capsules are intended for use only with the Aerolizer inhaler; they should not be swallowed.

To use the system, place a capsule in the well of the Aerolizer, then press and release the buttons on the side of the device. This will pierce the capsule. The medication is dispersed into the air stream when you inhale rapidly and deeply through the mouthpiece. Do not exhale into the device and do not use a "spacer" with this medication. Detailed instructions are supplied with your prescription. If you have any questions, ask your doctor or pharmacist.

One rare occasions, the capsule may break into small pieces, which could reach the throat or mouth during inhalation. You can reduce the chance of breakage by storing the capsules in a dry place, keeping them in their blister pack until just before use, and piercing them only once.

Be sure your hands are dry before handling the capsules, and be careful to keep the Aerolizer dry, too--do not wash any part of the device. Discard the aerolizer when your prescription is finished. Replace it with the new one that comes with each refill.

--If you miss a dose...

Take it as soon as you remember. If it is almost time for your next dose, skip the one you missed and go back to your regular schedule.

--Storage instructions...

Store at room temperature, away from heat and moisture. Leave the capsules in the blister pack until needed for use.

Foradil side effects

Side effects cannot be anticipated. If any develop or change in intensity, inform your doctor as soon as possible. Only your doctor can determine if it is safe for you to continue taking Foradil.

- *Side effects may include:*
  Abdominal pain, allergic reaction, anxiety, back pain, bronchitis, chest infection, chest pain, difficulty breathing, difficulty speaking, dizziness, dry mouth, fatigue, fever, headache, high blood sugar, high or low blood pressure, inability to sleep, increased sputum, indigestion, irregular heartbeat, itching, muscle cramps, nausea, nervousness, rash, runny nose, sinusitis, sore throat, stomach upset, tonsillitis, tremor, unwell feeling, upper respiratory and viral infections, worsening of asthma

Why should Foradil not be prescribed?

Foradil cannot be used for acute episodes of asthma that require intensive therapy. You'll also be unable to use Foradil if it gives you an allergic reaction.

Special warnings about Foradil

Your doctor will probably prescribe additional medications for use along with Foradil. Steroid inhalers such as Beclovent and Flovent fight inflammation in the airways. Short-acting airway openers such as Proventil and Ventolin relieve acute attacks. Be sure to use these medications exactly as prescribed. Do not change the dosage or stop using them without consulting your doctor.

Be sure to keep track of how often you use your short-acting inhaler for relief of acute asthma symptoms. Your doctor will use this information to help determine how well Foradil is working. Notify your doctor if your symptoms worsen, if you need more inhalations of the short-acting inhaler than usual, or if Foradil seems to be getting less effective. Keep track of your peak flow readings, too. Call your doctor if you notice a drop in this measurement of lung capacity.

Do not use Foradil more often than prescribed. Excessive use can cause heart irregularities. Use Foradil with caution if you have any kind of heart disorder or high blood pressure. Notify your doctor immediately if you experience palpitations, chest pain, rapid heart rate, or tremor.

Do not use Foradil in combination with Serevent, Advair Diskus, or other long-acting inhalers. They contain the same type of active ingredient and will provide no extra benefit. If you've been using a short-acting inhaler on a routine basis, you should stop using it regularly and reserve it for occasional relief of acute attacks.

Call your doctor immediately if you develop hives, rash, or swelling, or if you have an asthma attack that does not respond to your usual medication. Foradil has been known to cause allergic reactions and acute asthma attacks.

Possible food and drug interactions when taking Foradil

If Foradil is taken with certain other drugs, the effect of either may be increased, decreased, or altered. It is especially important to check with your doctor before

combining Foradil with the following:

Antidepressants categorized as "tricyclics," such as Elavil and Tofranil
Antidepressants classified as "monoamine oxidase inhibitors," such as Nardil and Parnate
Beta blockers (drugs such as Inderal and Tenormin that are used to control blood pressure and treat various heart conditions)
Steroids such as prednisone and hydrocortisone
Theophylline (Theo-Dur, Slo-Phyllin)
Water pills (diuretics) such as HydroDIURIL or Lasix

Special information if you are pregnant or breastfeeding

The possibility of harm during pregnancy has not been ruled out. Foradil is recommended for pregnant women only if the potential benefit outweighs the potential risk. Inform your doctor immediately if you are pregnant or plan to become pregnant.

It's not known whether Foradil appears in breast milk. Use this medication with caution if you are nursing.

Recommended dosage for Foradil

ASTHMA

For the long-term control of asthma in adults and children 5 years of age and older, the recommended dosage is 1 capsule every 12 hours. Do not use more than 2 capsules per day.

PREVENTION OF EXERCISE-INDUCED ASTHMA

For adults and children 12 years of age and older, the recommended dosage is 1 capsule at least 15 minutes before exercise. If a second dose is needed the same day, it must be taken at least 12 hours after the first dose. Do not exceed 2 capsules per day. If you are already taking Foradil on a regular twice-daily basis, do not take additional doses before exercise.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The usual dosage is 1 capsule every 12 hours. Do not use more than 2 capsules a day. If your customary dosage fails to provide the usual relief, check with your doctor immediately. Other treatments may have to be added to your regimen.

Overdosage

Any medication taken in excess can have serious consequences. If you suspect an overdose, seek medical attention immediately.

- *Symptoms of Foradil overdose may include:*
  Chest pain, dizziness, dry mouth fast or irregular heartbeat, fatigue, general feeling of illness, headache, heart palpitations, inability to sleep, muscle cramps, nausea, nervousness, seizures, tremor

Brand name:

Pulmicort Turbuhaler

Pronounced: PULL-mi-cort
Generic name: Budesonide

Why is Pulmicort Turbuhaler prescribed?

Budesonide, the active ingredient in Pulmicort Turbuhaler, is an anti-inflammatory steroid medication. Inhaled on a regular basis, Pulmicort helps prevent asthma attacks. It is sometimes prescribed in addition to oral steroids, and may reduce or eliminate the need for them.

Pulmicort Turbuhaler is used to treat asthma in adults and children over age 6. Children 12 months to 8 years of age can be treated with another form of budesonide, Pulmicort Respules, which is given by nebulizer. Both types of Pulmicort are preventive medicines. They will not relieve an acute or life-threatening episode of asthma.

Most important fact about Pulmicort Turbuhaler

Because steroids can suppress the immune system, people taking Pulmicort may become more susceptible to infections, and their infections could be more severe. If you are taking Pulmicort, avoid exposure to infectious diseases such as chickenpox and measles. If you are exposed, contact your doctor immediately.

How should you take Pulmicort Turbuhaler?

Use Pulmicort Turbuhaler exactly as directed. The effectiveness of Pulmicort Turbuhaler depends on its regular use. Your doctor will prescribe the lowest effective dose. Do not take more or less medication than the amount prescribed. When starting therapy, carefully read the instructions that come with the inhaler. Your asthma symptoms may begin to improve in 24 hours, although you may not see the maximum benefit for 1 to 2 weeks or longer. If your symptoms do not improve or get worse, contact your doctor.

Pulmicort Turbuhaler delivers a dose of medication in dry powder form. To assure the correct dose, the inhaler must be held in an upright position, with the mouthpiece on top, during priming and loading.

Before its first use, each new inhaler must be primed. To prime the inhaler, hold it upright and turn the brown grip fully to the right, then fully to the left until it clicks. Repeat this procedure a second time. The unit is now primed.

The inhaler must be loaded with medication immediately prior to each use. As you did when priming the unit, turn the brown grip fully to the right, then fully to the left until it clicks.

During inhalation, the inhaler must be held in an upright (mouthpiece up) or horizontal position. Do not shake the inhaler. Place the mouthpiece between your lips and inhale forcefully and deeply. The Pulmicort powder is then delivered to the lungs. Do not exhale through the inhaler.

You may not taste or sense any medication entering the lungs when inhaling from the Turbuhaler. This lack of sensation is not a cause for concern, and does not mean that you'll fail to receive the medication's benefits.

To decrease the risk of developing a fungus infection in the mouth, rinse it with water, without swallowing, after each dose. Do not use the inhaler with a spacer. Do not bite or chew the mouthpiece.

--If you miss a dose...

Take it as soon as you remember. If it is almost time for your next dose, skip the one you missed and go back to your regular schedule. Do not take 2 doses at once.

--Storage instructions...

Keep the Pulmicort Turbuhaler clean at all times. Replace the cover securely after each opening. Store with the cover tightened in a dry place at room temperature. Discard the unit when a red mark appears in the indicator window.

Pulmicort Turbuhaler side effects

Side effects cannot be anticipated. If any develop or change in intensity, inform your doctor as soon as possible. Only your doctor can determine if it is safe for you to continue taking Pulmicort.

- *Side effects may include:*
  Aching joints, back pain, cough, fever, flu-like symptoms, fungal infection in mouth, headache, indigestion, nasal and sinus inflammation, pain, respiratory infection, sore throat, weakness

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Why should Pulmicort Turbuhaler not be prescribed?

If you are allergic to budesonide, you cannot use Pulmicort. In addition, Pulmicort cannot be used to treat severe asthma attacks.

Special warnings about Pulmicort Turbuhaler

If you are switching to Pulmicort from an oral steroid medication, the doctor will be careful to reduce your oral dosage very gradually. Taking oral steroids suppresses the natural production of steroids by the adrenal gland, and it takes months for production to return to normal after the oral steroids are stopped. In the meantime, the body will be unusually vulnerable to stress.

There have been reports of death during and immediately after transfer from oral steroids to inhaled steroids, so your doctor will monitor you carefully during this period. People who have been taking high doses of oral steroids for an extended period of time are especially prone to problems, particularly when the oral steroids have been almost completely stopped. At that point, any stress from trauma, surgery, or infection (especially stomach or intestinal inflammation) is more likely to trigger adverse events.

If you experience a period of stress or a severe asthma attack during your switch to Pulmicort, you should begin taking your oral medication again (in large doses) and contact your doctor immediately. You should carry a medical identification card indicating that you may need additional medication during periods of stress or a severe asthma attack.

Transfer from oral steroids to Pulmicort may unmask allergic conditions previously controlled by those steroids, such as nasal inflammation, conjunctivitis (pinkeye), and eczema. Transfer from oral steroids may also be accompanied by withdrawal symptoms,

including joint or muscle pain, fatigue, and depression, even while Pulmicort is improving your asthma symptoms.

Like other inhaled asthma medications, Pulmicort occasionally triggers an asthma attack. If this occurs, immediately use a fast-acting inhaled bronchodilator, stop using Pulmicort, and contact your doctor. You'll need to switch to a different asthma medication. Also alert your doctor immediately if the usual doses of your fast-acting bronchodilator no longer work. You may need to take oral steroids for a while.

Steroid medications can stunt growth in children and teenagers. Your doctor will prescribe the lowest effective dose of Pulmicort in order to minimize this problem, and will monitor the child's growth carefully.

While using Pulmicort Turbuhaler, some people develop fungal infections in the mouth and throat. If this occurs, the doctor can prescribe antifungal medication while you continue to use Pulmicort. People with tuberculosis, ocular herpes simplex, or any untreated fungal, bacterial, viral, or parasitic infection should use inhaled steroids with caution. Caution is also in order if you have liver disease.

In rare instances, inhaled steroids have been known to cause glaucoma (increased pressure in the eye) and cataracts.

Possible food and drug interactions when taking Pulmicort Turbuhaler

If Pulmicort is taken with certain other drugs, the effects of either can be increased, decreased, or altered. It is especially important to check with your doctor before combining Pulmicort with the following:

Antibiotics such as clarithromycin (Biaxin) and erythromycin (E.E.S., Ery-Tab, PCE)
Antifungal medications such as ketoconazole (Nizoral) and itraconazole (Sporanox)

Special information if you are pregnant or breastfeeding

Pulmicort does not appear to harm the developing infant during pregnancy. Nevertheless, the possibility for harm cannot be ruled out. This medication should be used during pregnancy only if it is clearly needed.

Steroids make their way into breast milk. Because they could affect the nursing infant, you'll need to either discontinue breastfeeding or stop taking Pulmicort Turbuhaler.

Recommended dosage for Pulmicort Turbuhaler

ADULTS

The usual dosage depends on your previous treatments for asthma.

If you have previously been using only fast-acting bronchodilators, the usual starting dose is 200 to 400 milligrams twice a day. The maximum long-term dosage is 400 milligrams twice daily.

If you have previously been using inhaled steroids, the usual starting dose is 200 to 400 milligrams twice a day (or once daily in the morning or evening if your asthma has been well controlled). The maximum long-term dosage is 800 milligrams twice daily.

If you have previously been taking oral steroids, the usual starting dose is 400 to 800 milligrams twice a day. The maximum long-term dosage is 800 milligrams twice daily.

If you are taking oral steroids, you will continue to do so while starting Pulmicort Turbuhaler. After one week, the doctor will lower your dose of oral steroids, then gradually lower it further at one- or two-week intervals.

CHILDREN AGE 6 AND OLDER

As with adults, the child's usual dosage depends on previous treatments.

If the child has previously been using only a fast-acting bronchodilator the usual starting dose is 200 milligrams twice a day. The maximum long-term dosage is 400 milligrams twice daily.

If the child has previously been using inhaled steroids, the usual starting dose is 200 milligrams twice daily. (A once-a-day dose of 200 or 400 milligrams may be prescribed instead.) The maximum long-term dosage is 400 milligrams twice daily.

If the child has previously been taking oral steroids, the highest recommended dose is 400 milligrams taken twice a day. As with adults, the dosage of oral steroids will be gradually reduced while the child continues to take Pulmicort.

Overdosage

Excessive doses of steroid medications taken for long periods can stunt growth or cause a condition called Cushing's syndrome. Symptoms of this condition include weight gain, a "moon face," muscle wasting, weakness, and poor wound healing. If you think a problem is developing, check with your doctor immediately.

Generic name:

Fluticasone

Pronounced: flue-TICK-uh-zone
Brand names: Flonase, Flovent, Flovent Diskus, Flovent Rotadisk

Why is Fluticasone prescribed?

Flonase nasal spray is a remedy for the stuffy, runny, itchy nose that plagues many allergy-sufferers. It can be used either for seasonal attacks of hay fever or for year-round allergic conditions. Flonase is a steroid medication. It works by relieving inflammation within the nasal passages.

The Flovent, Flovent Rotadisk, and Flovent Diskus oral inhalers are used to prevent flare-ups of asthma. (They will not, however, relieve an acute attack.) They sometimes serve as a replacement for the steroid tablets that many people take to control asthma.

Most important fact about Fluticasone

Fluticasone is not an instant cure. It may take a few days for Fluticasone to start working; and you need to keep taking it regularly in order to maintain its benefits. While you are waiting for fluticasone to take effect, neither increase the dose nor stop taking Fluticasone.

How should you take Fluticasone?

Flonase is taken in the nostrils. For best effect, take the prescribed doses at regular intervals. First, blow your nose. Then shake the spray bottle gently, prime the pump 6 times if it hasn't been used during the past week, tilt your head back, press one nostril closed, and insert the tip of the bottle a short way into the other nostril. Spray once, pull the tip of the bottle away from your nose, and inhale deeply through the treated nostril. Repeat with the other nostril. Avoid spraying in eyes.

Flovent inhalation aerosol is taken orally. Shake the canister before each use. Take a deep breath and exhale. Then, as you begin to inhale, put your lips around the mouthpiece and depress the canister. Rinse your mouth with water after each use of the inhaler. Avoid spraying the contents in your eyes.

Flovent Rotadisk inhalation powder is also taken orally. Assemble the Rotadisk Diskhaler according to package instructions. To use, exhale, then place the Diskhaler mouthpiece between your teeth (without biting down) and close your lips firmly around it. (Be careful to avoid covering the small air holes on either side of the mouthpiece.) Breathe in through your mouth as deeply as you can, then hold your breath while you remove the Diskhaler. Continue to hold your breath as long as you comfortably can, up to a maximum of 10 seconds.

Flovent Diskus is a disposable oral inhaler that contains 60 inhalations. It must be kept dry. Do not wash it or attempt to take it apart. Always activate the inhaler in a level, horizontal position. Do not exhale into it. Do not use a spacer.

--If you miss a dose...

Take it as soon as you remember. If it is almost time for your next dose, skip the one you missed and go back to your regular schedule. Do not take 2 doses at once.

--Storage instructions...

Flonase may be stored at room temperature or in the refrigerator.

Flovent inhalation aerosol may be stored at room temperature away from sunlight, or in the refrigerator.

Flovent Rotadisk inhalation powder should be stored at room temperature in a dry place. Use the Rotadisk blisters within 2 months after opening the foil overwrap or before the expiration date, whichever comes first. Do not puncture the blisters until you are ready to use them in the Diskhaler.

The Flovent Diskus disposable inhaler should be stored at room temperature in a dry place, away from direct heat or sunlight. Once removed from its foil pouch, the device should be discarded after 2 months if not used up (after 6 weeks for the 50-microgram inhaler).

Fluticasone side effects

Side effects cannot be anticipated. If any develop or change in intensity, inform your doctor as soon as possible. Only your doctor can determine if it is safe for you to continue taking fluticasone.

- *Side effects may include:*
  Abdominal pain, aches and pains, agitation, aggression, anaphylactic reaction, back problems, bad taste in mouth, brittle bones, bronchitis, bruising, cataracts, congestion, cough, depression, diarrhea, dizziness, dry mouth, dry nose, eye problems, facial changes, fever, flu, headache, hives, hoarseness, indigestion, itching, loss of speech, mouth infection or swelling, nasal congestion, nasal irritation or burning, nasal sores, nausea, nosebleeds, rash, respiratory tract infection, runny nose, shortness of breath, sinus problems, sneezing, sore or irritated throat, stunted growth, swelling of the face and tongue, vomiting, weight gain, wheezing, worsening of asthma

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Why should Fluticasone not be prescribed?

If you have ever had an allergic reaction to Flonase or similar steroid inhalants such as Flovent, you should not take this medication.

Flovent is not to be used to treat status asthmaticus or acute asthma attacks.

Under very rare circumstances Flovent Rotadisk may cause an anaphylactic reaction in people with a severe milk protein allergy.

Special warnings about Fluticasone

If your symptoms do not improve after the first few days of fluticasone therapy, check with your doctor. Never take more than the recommended dose. High doses of steroid medications such as fluticasone can cause a condition known as Cushing's syndrome. Warning signs of this problem include weight gain and changes in the appearance of the face.

If you are being switched from an oral steroid tablet to fluticasone, you may experience joint pain, muscle pain, weakness, depression, or fatigue while your body adjusts to the

absence of steroid tablets and increases its own production of steroids. You may also experience eye inflammation, eczema, arthritis, and nasal inflammation.

People taking steroid medications run an increased risk of infections such as chickenpox and measles, and when an infection develops, it's more likely to be serious. If you've never had these diseases and have not been vaccinated against them, avoid anyone who may have them. If by chance you're exposed, contact your doctor immediately.

In rare cases, fluticasone can also cause a fungal infection in the nose and throat. And steroid treatment can also make an existing infection worse. Be sure the doctor is aware of any infections you may have, including TB and viral infections of the eye.

Steroid medications can stunt growth. If your child is on fluticasone therapy, the doctor should periodically check height and weight. In rare cases, people using Flovent have developed a serious lung condition marked by worsening asthma, heart problems, and numbness. If you start to notice any of these symptoms, report them to your doctor immediately.

If you develop wheezing and an asthma attack after inhaling any form of Flovent, use an emergency medicine such as an inhaled bronchodilator and call your doctor immediately. Also alert your doctor immediately if emergency medications fail to work as well once you've started Flovent therapy.

In rare cases, inhaled steroids such as Flovent have caused cataracts or increased pressure in the eye (glaucoma). Alert your doctor if you suffer from either problem.

If you have recently had a nasal injury or ulcer, or had surgery on your nose, you should wait until you are fully healed before using Flonase.

Possible food and drug interactions when taking Fluticasone

The risk of developing Cushing's syndrome and other side effects increases when you take other steroid medications while using fluticasone. Prednisone and dexamethasone are examples of oral steroid medications. Certain other asthma inhalers, skin creams, eyedrops, and eardrops also may contain steroids.

Also be sure to check with your doctor before combining fluticasone with ketoconazole (Nizoral) or HIV drugs known as protease inhibitors, including Agenerase, Crixivan, Fortovase, Norvir, and Viracept.

Special information if you are pregnant or breastfeeding

The effects of Fluticasone during pregnancy have not been adequately studied. If you are pregnant or plan to become pregnant, inform your doctor immediately. It is not known whether fluticasone appears in breast milk. If the drug is essential to your health, your doctor may advise you to stop nursing until your treatment is finished.

Recommended dosage for Fluticasone

FLONASE

Adults

The usual starting dose is 2 sprays in each nostril once daily. (Some doctors may prescribe 1 spray in each nostril every 12 hours.) Once your symptoms are under control, your doctor may reduce the dose to 1 spray in each nostril once daily.

Some people (12 and over) with seasonal allergies find that it's sufficient to use Flonase only on days when their symptoms flare up. If you use Flonase this way, take no more than 2 sprays per nostril on any given day.

Children

Flonase is not recommended for children under the age of 4. The recommended starting dose is 1 spray in each nostril once a day. If symptoms do not improve in a few days, the dose can be increased to 2 sprays in each nostril once a day, or 1 spray in each nostril twice a day. The dose should be reduced again once symptoms have subsided.

FLOVENT INHALATION AEROSOL

Adults and Children 12 and Over

If you are currently using an inhaled bronchodilator, the recommended starting dose is 88 micrograms twice a day. The maximum dose is 440 micrograms twice a day.

If you are currently using another steroid inhaler, the starting dose ranges from 88 to 220 micrograms twice daily. The maximum dose is 440 micrograms twice a day.

If you are taking oral steroid tablets, the doctor will start you at 880 micrograms of Flovent twice a day. He will slowly decrease your dose of steroid tablets, then lower your dose of Flovent.

Children Under 12

Flovent inhalation aerosol is not recommended.

FLOVENT ROTADISK AND FLOVENT DISKUS

Adults and Children 12 and Over

If you are currently using an inhaled bronchodilator, the recommended starting dose is 100 micrograms twice a day. The maximum dose is 500 micrograms twice a day.

If you are currently using another steroid inhaler, the starting dose ranges from 100 to 250 micrograms twice daily. The maximum dose is 500 micrograms twice a day.

If you are taking oral steroid tablets, the doctor will start you at 1000 micrograms of Flovent twice a day. He will slowly decrease your dose of steroid tablets, then lower your dose of Flovent.

Children 4 to 11 Years Old

For children already taking an inhaled bronchodilator or steroid, the recommended starting dose is 50 micrograms twice daily. The maximum dose is 100 micrograms twice a day.

Children Under 4

Not recommended.

Overdosage

Any medication taken in excess can have serious consequences. If you habitually use too much fluticasone, you run the risk of developing Cushing's syndrome (see "Special warnings about this medication").